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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,541	BRENNAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-16 and 20-29* is/are pending in the application.

4a) Of the above claim(s) *1-7,11-16 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

MC

DETAILED ACTION

Applicant's arguments filed 5-9-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 9, 10 and 17-19 have been canceled. claims 20-29 have been added. Claims 1-8, 11-16 and 20-29 are pending.

Election/Restrictions

New claim 29 is drawn to a method of identifying compounds using a transgenic mouse - a non-elected invention.

This application contains claims 1-7, 11-16 and 29 are drawn to an invention nonelected with traverse in the reply filed on 11-12-02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 8 and 20-28 are under consideration in this office action.

Specification

The amendment filed 5-9-05 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The addition of the application numbers into the paragraph beginning on pg 12, line 10, is new matter. No

support for the patent applications is found in the specification as originally filed. The applicants cannot newly incorporate entire patent applicants into the specification by reference. The disclosures of the applications contain a greater scope than originally contemplated in the instant application. It is not readily apparent that the disclosures of the applications newly cited were originally intended to be incorporated by reference in their entirety into the instant application. Applicant is required to cancel the new matter in the reply to this Office Action.

The application number in the paragraph beginning on pg 12, line 28, must be updated upon being allowed.

Claim Rejections - 35 USC § 101

Claim 8 remains rejected and claims 20-28 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility for reasons of record.

> REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf
>
> "Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.
>
> "Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence

of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.

(Paragraph bridging pg 32-33 of utility guidelines).

Claim 8 is directed toward a transgenic mouse whose genome comprises a null PAFR allele. Claims 24 and 25 require the mouse exhibits decreased anxiety in an open field test relative to a wild-type control mouse. Claims 26 and 27 require the mouse exhibits increased pain threshold in a hot plate test relative to a wild-type control mouse.

The specification teaches making PAFR -/- mice (pg 50-51).

The mice were tested in "open field testing" (pg 52, lines 16-20; Fig. 3). The specification does not distinguish the F and N generation in Table 1 or teach the strain of the wild-type control. The results of the open field test do not correlate to a useful phenotype because the "may have less anxiety in comparison to wild-type mice." In addition, only 2 PAFR -/- mice and 2 control mice were tested; one PAFR -/- mouse spent more time in the central region of the field than the control mouse, which is opposite of what is being claimed. Therefore, applicants' conclusion that the mice spent increased time in the central region of the field is flawed because the data is not statistically significant. Such an ambiguous phenotype is not specific to any disease or statistically significant because the difference observed is not significant and the mice merely "may" represent decreased anxiety.

The mice were tested in a "hot plate" test (pg 53, lines 1-5). The specification does not distinguish the F and N generation in Table 2 or teach the strain of the wild-type control. The results of the open field test do not correlate to a useful phenotype because the "may have a higher pain threshold in comparison to the wild-type mice." In addition, only 2 PAFR -/- mice and 2 control mice were tested. Therefore, applicants' conclusion that the mice displayed increase response latency to lick or fan their hind paw on the hot plate test is based on statistically insignificant data. Such an ambiguous phenotype is not specific to any disease or statistically significant because the difference observed is not significant and the mice merely "may" represent increased pain threshold.

The specification suggests using the mice to test compounds for neurological, neuropsychological or psychotic disease, but the specification does not disclose one specific neurological, neuropsychological or psychotic disease in humans linked to a disruption in PAFR (pg 20, lines 4-8). The specification does not disclose decreased anxiety is a behavioral, neurological, psychoneurological, psychotic phenotype. Decreased anxiety and increased pain threshold do not correlate to any disease in humans.

The specification suggests using the mice to identify agents that affect PAFR function (pg 19, lines 19-21). The mouse claimed cannot be used to identify agents that act on PAFR because the mice do not express PAFR.

It was "well-known" in the scientific community at the time of filing to knock out a gene in a mouse in an attempt to determine its function; however, it was also "well-known" that the mouse may only provide clues to the function of the gene and that the mouse may not be capable of determining the function of the gene. While the mouse may have "scientific utility," "scientific utility" is not the same as "patentable utility" or a "well-established" utility.

The utility guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention (with decreased anxiety or increased pain threshold) as a model of disease. Further study would be required to determine the function of the disrupted gene. The overall phenotype of the applicants' mice does not correlate to any disorder; therefore, further study would be required to determine how to use the mice to study a disorder. Thus, using the mice claimed for further research is not a "substantial utility."

Using the mice to identify the function of the knocked out gene is not a "substantial utility" or "specific utility" because the phenotype may be caused by other proteins compensating for the deleted gene. Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility"

because the phenotype may be a result of other compensating proteins and not the knocked out gene.

Using the mice to identify agents capable of altering a phenotype would require further research and is not a "substantial utility" or "specific utility" because the mouse may not be capable of identifying agents capable of treating disease. Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-). Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or GPCR-like protein in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to determine how to use such an agent identified using the mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not the GPCR-like

protein itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice.

The function of a gene may not be found by studying a knockout mouse. Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) used knockout mice that had increased anxiety further study to determine the function of $GABA_B$ receptor. Mombereau did not teach how to use mice with decreased anxiety as claimed. In addition, Mombereau did not determine the function of the $GABA_B$ receptor. Mombereau administered compounds known to antagonize $GABA_B$ receptor (found in *in vitro* assays, not in the mice) to the mice. Mombereau concluded that the mice merely confirmed $GABA_B$ was involved in a molecular pathway relevant for the manifestation of anxiety or depression. Mombereau did not determine the function of $GABA_B$ receptor using the $GABA_B$ -/- mice. Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology. Nonetheless, the current data show that even such mice can still be utilized to give important indicators of the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm

the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col. 1, 2nd full ¶, line 1-4). Therefore, using a mouse to merely obtain clues of the role of a protein in a molecular pathway of anxiety or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of the protein within the pathway.

Overall, the mice claimed do not have a "well-established utility" because using the mice for further research (to determine how to use the mouse as a model of non-disclosed disease, to determine the function of the gene or to identify agents capable of altering a phenotype) is not a "specific utility" or "substantial utility."

Applicant argues the mice have a well-established utility because a person of ordinary skill would immediately appreciate why the knockout mice were useful to define the function and role of the disrupted gene. Applicant points to an NIH report from 2004, Austin (Nature Genetics, 2004, Vol. 36, No. 9, pg 921-924), The Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)), Gene VII (Lewin, Oxford University Press (2000)), Joyner (Gene Targeting: A Practical Approach, Oxford University Press, 2000), Matise (Production of targeted embryonic stem cell clones in Joyner) and Crawley (What's wrong with my mouse, Behavioral phenotyping of transgenic and knockout mice, Wiley-Liss, 2000) to establish the mice had "well-established" utility. Applicant's arguments are not persuasive.

First, the NIH report and Austin were not available until 2004 and cannot be used to establish what was "well-established" at the time of filing.

Second, while the NIH report suggests knockout mice may be models of disease, a mouse with symptoms increased startle response as described in the specification is opposite of schizophrenia.

Lastly, the references merely suggest using knockout mice to study the function of targeted genes, which does not rise to the level of a substantial utility according to the utility guidelines. The NIH report states knockout mice can be used to elucidate gene function. Austin states null-reporter alleles should be created as a starting point for studying the function of every gene. The Molecular Biology of the Cell states mutant mice can be an invaluable tool for investigating gene function. Gene VII states knockout mice are used to investigate directly the importance and function of a gene. Joyner states gene targeting in ES is used to study gene function in a mammalian organism. Matise states knockout ES cells can be used to study gene function in cell culture and in vivo. Crawley states knockout mutations provide a means for understanding gene function. None of references teach the mice will determine the function of the gene. Applicants have used the mice in expression analysis and phenotype analysis tests, but applicants have not determined the function of the gene. Simply using the mice for further research of the PAFR gene is not a specific or substantial utility. None of the references teach a specific or substantial utility for mice with a disruption in a gene.

The function of the gene may never be determined from the knockout mouse Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility" (see utility guidelines, "[T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": A. Basic research, i.e. "studying the properties of the claimed product itself or the mechanisms in which the material is involved," may never reveal the function of the PAFR gene and least significant further study would have been required to use the knockout mice to determine the function of the PAFR gene. A mouse requiring significant further research to determine the function of the gene and that only provides a clue to the genetic pathway to which the gene may be involved does not rise to the level of a specific and substantial "well-established utility" as set forth by the utility guidelines.

Applicants compare the mice claimed to gas chromatographs, screening assays and nucleotide sequencing methods. Applicant's arguments are not persuasive. Gas

chromatographs, screening assays and sequencing have specific, credible and substantial utilities. Gas chromatographs separate the chemical components of a compound and identify them. Screening assays have various functions, but may be used, for example, to determine the amount of protein expression in a population of cells. Sequencing methods provide the nucleotide sequence of a nucleic acid molecule. Unlike gas chromatographs, screening assays or sequencing methods, the mice claimed may be used to generate data, but the data may not reveal the function of the gene or provide any substantially useful information. Evidence is provided by applicant's own data in which expression analysis and behavioral analysis generated data, but the data reveal the function of SEQ ID NO:1. Further research would be required to determine the function of SEQ ID NO:1 using the data provided by applicants. The utility guidelines state using a product for further research is not a "substantial" utility. In this case, the expression analysis does not even provide a clue as to the function of SEQ ID NO:1 in the anxiety or pain pathway. Therefore, using the mouse claimed as a research tool, specifically for expression analysis, does not provide any substantial utility.

Applicants argue the mice have been ordered by at least four pharmaceutical companies. Applicants provide a declaration by Robert Driscoll establishing such sales. Therefore, applicants conclude that those of skill would recognize the utility of the mice. Applicant's argument is not persuasive. Sales may be evidence to overcome a 103 obviousness rejection, but there is no case law that establishes that "sales" are evidence of patentable utility. Evidence of

sales is not evidence the mice have a "well-established" utility or a "specific utility" or a "credible utility" because the data generated using the mice may not provide a clue to the function of SEQ ID NO:1. Therefore, proof of sales does not establish the mice will provide data that rises to the level of a specific, substantial utility as evidenced by applicant's data. In fact, proof of sales does not establish applicants had a substantial or specific use for the mice at the time of filing; a substantial or specific use for the mice may have been determined since the time of filing but is not readily apparent from the specification as originally filed. Evidence that the mice have been ordered since the time of filing is inadequate to prove the mice had a specific and substantial utility at the time of filing.

Applicants argue mice actually being used must have a real world use. Applicant's argument is not persuasive. Just because the mice are in use in the industry in 2005 does not mean the specification as originally filed disclosed a "real world use." The industry may have determined how to use the mice since the time of filing. Furthermore, just because the mice are used does not mean the use has substantial, specific and credible utility. The utility guidelines indicate a "real world use" must be substantial, specific and credible. In this case, merely studying a gene using a knockout mouse is not a substantial "real world use" because the gene does not have a patentable utility, because further research does not constitute a patentable utility and because the mouse may never reveal the function of the gene. Nowhere has applicants pointed to one

specific assay that has a substantial use in which the mice claimed are used by the industry or that correlates the data to a specific disease condition or gene function. Nowhere has the applicant pointed to one piece of data that can be correlated to a disease state or that is capable of revealing the function of the PAFR gene. Further study of mice would have been required to determine how to use the mouse of Applicant's invention as a model of disease. Therefore, it is not readily apparent that the mice claimed have a "real world use" that is substantial, specific and credible.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure for mice with the phenotype described. Applicants cite Austin (cited above) and Doetschman (Lab. Animal Sci., 1999, Vol. 49, pg 137-143) who teach mice have much in common with humans and that knockouts will provide "information concerning gene function...." Applicants' arguments are not persuasive. Not all claims are limited to mice with a phenotype. Mice with decreased anxiety or increase pain threshold are not models of humans with any disease. Specifically, decreased anxiety is not a disease state. The examiner has provided ample reasoning and evidence why those of skill in the art at the time of filing would doubt why each phenotype fails to have substantial utility. The examiner has provided ample reasoning why each asserted utility fails to have substantial and/or specific utility. Even applicants' own further research, i.e. the expression, physical and behavioral analysis did not reveal the function of the PAFR gene. Significant further research in this case is required to use the mice with the phenotypes described to determine the

function of the PAFR gene. Therefore, using the mice with the phenotypes described to determine clues to the function of the PAFR gene does not constitute a patentable utility. One may never find a drug capable of treating anxiety or increased pain threshold using the mouse claimed. In *Brana*, the applicants disclosed compounds that were effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The mice claimed in the instant application do not correlate to the compounds described by Brana because are not used for treating disease.

Applicants argue that according to the "database commercial database protocol, comparison of mice was made with age, gender and strain-matched control mice." Applicants' argument is not persuasive. No such conclusion can be made from the specification as originally filed, particularly the phenotypic analysis on pg 52, lines 14-20 and Table 1.

Applicants point to Table 1 on pg 52, which "clearly shows the F and N generation (either F2N0 or F2N1)." Table 1 includes numbers for F and N; however, the specification does not distinguish F and N so that the breeding and genotype of the mice can be determined. It is not readily apparent how F2N0 differs from F2N1 or how F and N differ. It cannot be concluded from Table 1 that -/- knockout mice were compared with age, gender and strain-matched control mice.

Applicants argue mice that spend increased time in the open field have decreased anxiety because normal mice spend more time in corners. Applicants' argument is not persuasive. Mice that spend increased time in the open field may

simply be bolder as described on pg 23, lines 26-27 and in applicants' arguments or they may be hyperactive. Thus, there is not a direct correlation to increased time in the open field and "decreased anxiety" as claimed because the observation may be a result of another pathway, i.e. a "boldness," hyperactivity, intelligence or instinct pathway .

Applicants argue 3 F2N0 +/+, 9 F2N1 +/+, 6 F2N0 -/-, and 11 F2N1 -/- mice were compared in the open field test as determined from the "Count" column of Table 1 (pg 52). Applicants' argument is persuasive. However, the difference between the F2N0 and F2N1 +/+ mice and between the F2N0 and F2N1 -/- mice cannot be determined. F2N1 +/+ control mice had increased time (34.36) as compared to F2N0 -/- mice (18.35), which is opposite of the phenotype claimed.

Applicants argue mice with a change in pain threshold have a real world use for evaluating a nociceptive disorder. Applicants' argument is not persuasive. Applicants have not described one specific nociceptive disorder that correlates to increased pain threshold in a hot plate test. Nor have applicants correlated the disruption of the PAFR gene with a nociceptive disorder.

Applicants argue 6 F2N0 +/+, 12 F2N1 +/+, 8 F2N0 -/-, and 11 F2N1 -/- mice were compared in the hot plate test as determined from the "Count" column of Table 2 (pg 53). Applicants' argument is persuasive. However, the difference between the F2N0 and F2N1 +/+ mice and between the F2N0 and F2N1 -/- mice cannot be determined.

Applicants argue heterozygous mice can be used to identify drugs because they express the PAFR gene. Applicants' argument is not persuasive. Nowhere does the

specification suggest using heterozygous mice to identifying drugs based on the expression of the PAFR protein. Heterozygous mice are only described as a means of obtaining the homozygous mice used in the physiological and behavioral tests. Homozygous mice cannot be used for protein binding assays because they do not express PAFR. Applicants have not pointed to any specific assay for identifying drugs using homozygous mice that do not express PAFR.

Applicants argue mice with scientific utility must have patentable utility. Applicants' argument is not persuasive. Applicants underlining in the section of the MPEP relating to "substantial utility" is misleading and ignores the rest of the sentence. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. The data obtained by applicants, for example, leave the skill artisan to conduct further research to determine a "real world" context of use for the mice because the data does not identify any compounds capable of treating disease or reveal the function of the gene. The specification does not teach how to conduct the "further research" so that the mice may be used to identify compounds capable of treating disease or to identify the function of PAFR.

Applicants argue Olsen does not support the examiner's position because Olsen states '"gene targeting is useful in delineating the contribution of a given gene product to phenotypic characteristics" even though "some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype"'. Olsen concludes that "the use of mutant and knockout mice has

aided understanding of the roles of GAD and GABAR in the intact mammalian organism with much promise for additional information to come" (Olsen at 91)." Even with respect to mice having increased lethality, Olsen states: "[t]he γ2 and β3 subunit knockouts are associated with early postnatal lethality but have nonetheless provided considerable new information about their importance, include relevance to neurodevelopment, synaptogenesis, and possibly human disease." Applicant's arguments are not persuasive. A mere association of a gene with "early postnatal lethality" is not specific to any disease or substantial because it does not clarify the "association" or the function of the gene. Olsen supports the ability to use knockout mice to gain clues to a gene's function, but the "clues" described by Olsen do not rise to the level or a substantial, specific and credible utility.

Applicants argue Bowery does not support the Examiner's position. Bowery discusses use of hot-plate, tail-flick and paw pressure protocols to evaluate acute pain behavior in GABA-B1 null mutant mice. Bowery concludes "it is likely that GABA-B mediated effects do indeed exert a tonic control of nociceptive processes in the naïve animal" (pg 255, col.2). Applicant's argument is not persuasive. Bowery teaches knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or PAFR protein in the instant application), but such a use is not substantial because the agent may not be capable of treating disease. Further research would be required to determine how to use such an agent identified using the

mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not the PAFR protein itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice. Using mice to identify agents that merely bind to a receptor as described by Bowery without identifying agents that treat disease does not rise to the level of a substantial utility.

Applicants argue Mombereau provides a well-established use for the mice claimed. Applicant's argument is not persuasive because Mombereau was not available until 2004.

Applicants argue Schoenwald related to an anticipation rejection and does not relate to the utility requirements. Applicants' argument is not persuasive as the issue at hand related to utility. The decision established that an anticipation reference does not have to provide a utility for the rejection to be proper. In other words, a product known in the art may not have utility. In this case, the mouse claimed might only provide a clue to a pathway in which SEQ ID NO:1 is involved. This is not a specific utility because results from the tests may only indicate SEQ ID NO:1 is involved in a pathway. Decreased anxiety or increased pain threshold as determined by the open field test or hot plate test

provides only a clue that SEQ ID NO:1 is generically associated with hyperactivity, anxiety or pain. SEQ ID NO:1 may be involved in a hyperactivity pathway influenced by numerous proteins. Assuming further study of the mouse will elucidate the function of SEQ ID NO:1, the amount of research required to do so, especially to determine the function of SEQ ID NO:1 within a pathway, would be significant. The specification does not guide those of skill to any particular blaze marks so that one of skill would know the assays required to determine the function of SEQ ID NO:1.

Applicants argue the mice can be used for "expression analysis." Applicants' argument is not persuasive. The specification does not teach what promoter is driving the LacZ reporter gene; therefore, it cannot be determined how expression of LacZ is relevant to determining anything about SEQ ID NO:1 (see Example 1). More importantly, if LacZ were operably linked to the gene's promoter, the expression analysis would not reveal the function of the gene. The specification does not teach how to use the expression analysis data to determine the function of the gene. Therefore, using the mice claimed in expression analyses does not have substantial utility.

Claim Rejections - 35 USC § 112

Enablement

Claim 8 remains rejected and claims 20-28 are rejected under 35 U.S.C. 112, first paragraph for reasons of record. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for reasons of record.

Applicants refer to the arguments in the utility rejection, which have been addressed above.

New Matter

Claims 8 and 20-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "null platelet-activating factor receptor (PAFR) allele" in claim 1 remains new matter because the phrase does not have support in the specification as originally filed. The phrase "null allele" was known in the art as an experimental strategy that ablates the function of a target gene by introducing a selectable marker gene (Hasty, Definition of "null allele" in Hasty (Chapter 1 ("Gene targeting, principles, and practice in mammalian cells") in Joyner, Gene Targeting: A Practical Approach, Oxford Univ. Press, 2000, pg 1, provided by applicants). However, the definition known in the art by Hasty has a greater breadth than the PAFR disruptions described on pg 3,

lines 12-19, and pg 7, lines 3-11 (defining "disruptions" as encompassing mutations made by homologous recombination). Therefore, the specification as originally filed does not contemplate the genus (or species when viewed in context of the genus of "disruptions" described on pg 7, lines 3-11) of "null alleles".

The term "selection marker" in claim 22 is new matter. No support can be found for the genus of "selection markers" can be found in the specification as originally filed.

Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 20-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The new phrase "transgenic mouse whose genome comprises a null PAFR allele" in claim 1 is indefinite. It is unclear if the phrase is limited to a mouse without any of the PAFR gene, or if the phrase encompasses a mouse without any of the coding region of the PAFR gene, a mouse with a disruption in the PAFR gene, wherein said disruption does not allow production of functional PAFR, or a mouse with a disruption in the PAFR gene, wherein said disruption causes less than normal amounts of function PAFR. The metes and bounds of what applicants consider a "null" allele cannot be determined.

A mouse having a "null endogenous PAFR allele," "wherein the PAFR allele

encodes for mRNA comprising SEQ ID NO:1" in new claim 28 is indefinite because the claim does not make sense. An allele cannot be a "null allele" and encode SEQ ID NO:1 at the same time. A null allele cannot encode the full length mRNA of SEQ ID NO:1 as claimed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

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PRIMARY EXAMINER